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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,236	03/04/2002	Christine Dingivan	10271-053	7180

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EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
09/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/091,236	DINGIVAN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 07/03/2007 has been entered.

Applicant's amendment, filed 07/03/2007, has been entered.

Claims 1-70 have been canceled.

Claims 71-76 have been added.

As indicated previously, applicant's election of Group I and to prosecute the species wherein the alphavbeta3 antagonist is VITAXIN / anti-alphavbeta3 antibody and the TNF-alpha antagonist is REMICADE / anti-TNF-alpha antibody in the Reply, filed 12/1205 and the disease "rheumatoid arthritis" in the Reply, filed 3/31/06, has been acknowledged.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's amendment, filed 07/03/2007.

The rejections of record can be found in previous Office Action, mailed 07/03/2007.

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. 1.75(d)(1) and M.P.E.P. 608.01(l). Correction of the following is required:

Upon a review of the instant specification, the recitation of "about" in claims 73-74 in terms of the dosages claimed is not readily apparent (e.g., see Section 5.4 Compositions and Methods of Administering Combination Therapy, particularly pages 128-134).

Applicant is requested to identify the written support for the recitation of "about" in claims 73-74 in terms of the dosages claimed.

Alternatively, applicant should amend the instant specification to provide the proper antecedent basis for the recitation of "about" in the instant specification as filed.

It is noted that the original claims appear to provide the proper antecedent basis for the recitation of "about" in the context of the claimed dosages.

4. Upon consideration of applicant's amended claims, filed 07/03/2007, the previous rejections under 35 U.S.C. § 112, second paragraph, with respect to the recitation of "immunomodulatory agents", "anti-inflammatory agents", "immunomodulatory agents is a small organic molecule" "VITAXIN" and "REMICADE", "etaraizumab" and "infliximab", have been withdrawn.

5. Upon consideration of applicant's amended claims, filed 07/03/2007, the previous rejection under 35 U.S.C. § 112, first paragraph, written description with respect to the recitation of "etaracizumab" and "infliximab" (and non-elected "etanercept).

6. Upon consideration of applicant's amended claims in conjunction with Exhibit A (product information from the Physicians Desk Reference, 55th Edition, 2001; 1449) , filed 07/03/2007, the previous rejection under 35 U.S.C. 112, first paragraph, enablement, with respect to the recitation of "etaracizumab" and "infliximab" (and non-elected "etanercept).

7. Claims 71-76 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Feldman et al. (U.S. Patent NO. 6,270,766) in view of by Huse (U.S. Patent No. 6,596,850), The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 416-423) and Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456) essentially for the reasons of record.

Applicant's arguments in conjunction with MPEP 2143, filed 07/03/2007, have been fully considered but have not been found convincing essentially for the reasons of record.

Again, applicant submits that the there is no motivation in the prior art to modify or to combine specific treatment regimes to meet the claimed methods.

With respect to the teachings of Feldman et al., applicant asserts
that Feldmann et al. is limited in its scope as it only teaches the combination of TNF-a antagonist therapy with methotrexate to alleviate TNF-a mediated diseases;
that Feldman also does not teach nor suggest that one could target integrins, through an antagonist to alleviate the signs of a TNF-α mediated disease (see abstract, page 4, ln 19-36, page 5 ln 1-33 of the instant specification);
that Feldman is deficient by containing no teaching of targeting adhesion, migration, or angiogenesis, known physiological properties influenced by αvβ3 integrins, in order to treat a TNF-α mediated disease and
that Feldman also does not contain any teaching or suggestion of combining αvβ3 specific antibodies or antigen binding fragments thereof and infiximab or antigen binding fragments thereof in a method of treating rheumatoid arthritis as claimed by the current invention.

Applicant asserts that Huse does not cure the above deficiencies of Feldman. Huse does not teach the specific combination of therapies, namely, the αvβ3-specific antibody or an antigen binding fragment thereof and infliximab or an antigen binding fragment thereof in a method of treating rheumatoid arthritis, as claimed by the current invention.

With respect to the secondary references and combination therapy,
applicant asserts that The Merck Manual (pages 416-423) and Strom et al. (pages 451-456) either relate to conventional immunosuppressive therapy or teach immunosuppressive therapy during organ transplantation, a condition independent of the teaching of the instant specification and of the claimed invention and
add little to the teachings of Feldmann et al. and Huse.

Applicant also submits the claimed methods involves the systemic treatment of a soluble factor differs greatly from the mechanism that αvβ3-specific antibodies employ, which is directly targeted to newly formed vasculature, such as at the site of arthritis.

Again, one cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. See In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

For example, in contrast to applicant's assertions concerning the absence of a relationship between TNF-α and αvβ3
It is noted that Huse does teach that Vitaxin was found to inhibit TNF-α- induced angiogenesis in a dose dependent manner (see Example IV, Vitaxin-Mediated Inhibition of αvβ3 in Animals Models on columns 35-37, particularly column 35, paragraph 4).

Further as noted previously, Feldmann et al. does describe that other therapeutic regimens and agents can be used in combination with the therapeutic administration of TNF antagonists or other drugs that suppress the immune system (e.g., see Detailed Description of the Invention, particularly, column 4, paragraph 5).

Also as noted previously, applicant's assertions are inconsistent with the disclosure of the instant specification, which acknowledges that any immunomodulatory agent well-known to one of skill in the art may be use in the methods of the invention (e.g., see page 61, paragraph 1).

In a similar fashion, applicant's arguments and the examiner's rebuttal with respect to applicant's assertions that Huse does not teach the claimed combination of therapies or the specific immunomodulatory agents are essentially the same addressed of record as addressed with respect to the teachings of Feldmann et al.

Also, consistent with the teachings of Feldmann et al. and the disclosure of the instant specification as-filed, Huse does teach that Vitxain/LM609-specific antibodies can be administered with other compositions which can inhibit enhance or supplement the treatment or reduction in the severity of an αvβ3-mediated disease (e.g., see Detailed Description of the Invention, particularly column 26, paragraph 2).

Applicant again asserts that at the time of filing, no reasonable expectation of success for the teachings of claimed invention were evident from the cited references.

However, applicant does not provide sufficient objective evidence to support the assertions of non-obviousness.

As indicated herein, once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. See In re Keller, 208 USPQ 871, 882 (CCPA 1981).

This applicant has not done, but rather merely asserts that the prior art does not provide sufficient suggestion or motivation to combine the prior art to treat inflammatory disorders / autoimmune diseases, including rheumatoid arthritis, with the combination of TNFα antagonists such as anti-TNFα antibodies and alphavbeta3 antagonists such as LM609/Vitaxin-specific antibodies and does not address the teachings of the references individually and not their teachings individually or in combination. Also, as noted herein, applicant's arguments are inconsistent with applicant's arguments in addressing the rejections under 35 USC 112, first and second, paragraphs, wherein applicant appears to acknowledge the well known use and characteristics of TNFα antagonists such as the anti-TNFα antibody infliximab and alphavbeta3 antagonists such as the humanized LM609/Vitaxin- antibody at the time the invention was made.

When considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA).

Further, in response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the teachings of combined references pertaining to the ability to inhibit rheumatoid arthritis with either TNFα antagonists such as anti-TNFα antibodies or alphavbeta3 antagonists such as LM609/Vitaxin-specific antibodies, including combination therapies, which encompassed conventional practices at the time the invention was made, would have led one of ordinary skill in the art at the time the invention was made to combine the references to address similar and well known therapeutic endpoints associated with ameliorating or treating inflammatory disorders / autoimmune diseases, including rheumatoid arthritis with an expectation of success in the absence of objective evidence to the contrary.

Given the combined teachings, one of ordinary skill in the art at the time the invention was made would have been motivated and would have had a reasonable expectation of success of providing multiple immunosuppressive agents in the treatment of rheumatoid arthritis, as commonly practiced at the time the invention was made, and as taught by the primary and secondary references. Also, it is noted that the teachings of both Feldman et al. and Huse are consistent with this common practice, as both teachings teach combination therapies with either TNFα antagonists such as anti-TNFα antibodies or alphavbeta3 antagonists such as anti-alphavbeta3 antibodies, including their combination with known therapeutic regimens for the disease targeted.

Also, it was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

The claimed limitations were well within the purview of an ordinary artisan at the time the invention was made. The various dosages and modes of administration encompassed by the claimed methods (e.g. see claims 73-75) appear to the same or nearly the same as set above, particularly in the teachings of Feldman et al. (e.g. see Administration on column 18, to meet the needs of the patient and the particular disease.

It is obvious to optimize result effective variables known to impart desired endpoints. To determine optimum concentrations of reactants in within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425.

Further, if routine experimentation by one of ordinary skill would have led to the optimum compositions for treating patients in need, the claimed dosages were obvious, even though the results obtained by the composition are unexpectedly high (Indiana General Corp. v. Krystinel Corp. (CA 2 1970) 421 F2d 1023, 164 USPQ 321). See also In re Boesch, 617 F.2d 272,205 USPQ 215 (CCPA 1980) in this regard.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the combination of the prior art disclosure in motivating the ordinary artisan to administer to patients with rheumatoid arthritis as patients in need of being treated for inflammatory conditions by targeting TNFα and/or αvβ3.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Applicant's arguments have not been found persuasive.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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